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| 10/726,198 | 12/02/2003 | Constance M. John | 3157.00011 | 3458 |

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| EXAMINER | |
|---|---|
| REDDIG, PETER J | |
| ART UNIT | PAPER NUMBER |
| 1642 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/726,198 | JOHN ET AL. | |
| | Examiner | Art Unit | |
| | Peter J. Reddig | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 8-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/2/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. The response filed on January 22, 2007 to the restriction requirement of August 7, 2006 has been received. Applicant has elected Group I claims1-7, SEQ ID NO: 1, and the species cancer for examination. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse MPEP 818.03(a).

2. Upon review and reconsideration, the election of SEQ ID NO: 1 will be treated as an election of species given that claim 1 is generic to N-terminally truncated forms of galectin-3. The claims will be examined as drawn to N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof. Additionally, the intended uses for the composition of claim 4 will be rejoined because the intended use is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredient *per se*, the N-terminally truncated galectin-3 which has a sequence according to SEQ ID NO: 1 and analogues thereof, see MPEP 2111.02 [R-3]-II.

3. Claims 1-24 are pending.

4. Claims 5, 6, and 8-24 are hereby withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

5. Claims 1-4 and 7, as drawn to N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof are currently under consideration.

6. An examination of this application reveals that applicant is unfamiliar with patent prosecution procedure. While an inventor may prosecute the application, lack of skill in this field usually acts as a liability in affording the maximum protection for the invention disclosed.

Applicant is advised to secure the services of a registered patent attorney or agent to prosecute the application, since the value of a patent is largely dependent upon skilled preparation and prosecution. The Office cannot aid in selecting an attorney or agent.

A listing of registered patent attorneys and agents is available on the USPTO Internet web site http://www.uspto.gov in the Site Index under "Attorney and Agent Roster." Applicants may also obtain a list of registered patent attorneys and agents located in their area by writing to the Mail Stop OED, Director of the U. S. Patent and Trademark Office, PO Box 1450, Alexandria, VA 22313-1450

***Priority***

7. Examiner has established a priority date of 12/2/2003 for claim 4 of the instantly claimed serial number 10/726,198 because claim 4 as currently constituted recites "The composition according to claim 1 for use in treating . . . **atherosclerotic cardiovascular disease** . . ." and a review of the parent applications does not reveal the claimed limitation.

Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Examiner has established a priority date of 6/10/2002 for claims 1-3 and 7 of the instantly claimed serial number 10/726,198 and a review of PCT/US02/18478 revealed the claimed limitations.

8. This application repeats a substantial portion of prior Application No. 09/877,790, filed June 8, 2001, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the

benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

***Oath/Declaration***

9. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration filed September 30, 2004, see p. 4. See 37 CFR 1.52(c).

***Drawings***

10. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Fig. 1A and B, Fig. 4A, B, and C, and Fig. 10 A, B, and C. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

11. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Fig. 11 A-D, Fig. 12 A-D, Fig. 13 A-C, Fig. 14 A-C, Fig. 15 A-C. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Specification***

12. The disclosure is objected to because of the following informalities: The reference to Kim 1999, #955 on p. 56, line 10 does not clearly identify the reference.

Appropriate correction is required.

13. The specification is further objected to on page 34-lines 27 and 28, page 59-lines 15 and 16, and page 82 for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. SEQ ID NOs. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or

1.825(b) or 1.825(d). *Failure to supply the appropriate sequences identification numbers in response to this action will be considered non-responsive.*

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-4 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "truncated" in claims 1-3 is a relative term which renders the claim indefinite. The term "truncated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One cannot determine where galectin-3 is N-terminally truncated, thus one of skill in the art cannot determine which galectin-3 fragment is claimed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-4 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a polypeptide consisting of SEQ ID NO: 1, does not reasonably provide enablement for a composition comprising N-terminally truncated galectin-3 according to SEQ ID NO: 1 and analogues thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a composition comprising an effective amount of N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof and a pharmaceutically acceptable carrier.

This means that the claims are inclusive of fragments and variants of SEQ ID NO: 1 because the transitional phrase "according to" is an open-ended term that does not limit the claims to a protein comprising all of the amino acids of SEQ ID NO: 1 and is inclusive of fragments and variants of SEQ ID NO: 1 given that the specification teaches that that the truncated proteins of the present invention which "correspond to" a N-terminally truncated galectin-3 are, in general, homologous amino acid sequences of SEQ ID NO: 1 (see p 24, lines 11-14). Thus claim 2 is drawn to "a" sequence according to SEQ ID NO: 1 which reads on 2 amino acids of SEQ ID NO: 1.

Furthermore, the specification teaches that the present invention provides an N-terminally truncated variant having at least the qualitative biological activity as defined herein and having, for example, at least about 75%, and preferably at least 90%, amino acid homology with the portions that it contains of the polypeptide of SEQ ID NO: 1. The specification teaches that the variant amino acid sequence preferably shares at least 80%, more preferably, greater than 85% sequence homology with the portion that it contains of the sequence of SEQ ID NO: 1. The specification teaches that however, a galectin-3 variant or related compound can exhibit less than 50% sequence homology with the sequence of SEQ ID NO: 1 and still retain the characteristics of a galectin-3 variant as described herein (see p. 24, lines 15-25). It is noted, however, that none of these teachings are in any way limiting.

One cannot extrapolate the teaching of the specification to the scope of the claims because the claims encompass unknown and undefined analogues and fragments of the N-terminally truncated galectin-3/SEQ ID NO: 1 and the unpredictability of protein biochemistry is well known in the art.

In particular, Merck Source/Dorland's Illustrated Medical Dictionary (www.mercksource.com/pp/us/cns/cns_home.jsp) teaches that an analogue " . . . may have a similar or opposite action metabolically". Furthermore, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is

extremely complex (col. 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Given the lack of teaching of amino acid residues critical to the function of the claimed N-terminally truncated galectin-3, in view of the unlimited and undefined alteration in N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof contemplated in the specification and claimed, the function of the broadly claimed N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof could not be predicted and would not be expected to be the same as that of an unaltered SEQ ID NO: 1 and the functions and

effects of analogues, fragments, and variants could not be extrapolated from the functions and effects of SEQ ID NO: 1 with a reasonable expectation of success.

Clearly, given the teachings of Bowie et al, Lazar et al, and Burgess et al the effects of undefined changes in the N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof could not be predicted. Furthermore, the claims require that the composition be an effective amount of N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof, but the specification does not teach which amino acids that are critical for the claimed protein to be functionally effective. Thus the specification provides neither information nor guidance on how to make the broadly claimed N-terminally truncated galectin-3. Thus, it would take undue experimentation for one of ordinary skill in the art to practice the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as

contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

15. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claims 3, 4, and 7 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a composition comprising an effective amount of N-terminally truncated galectin-3 according to SEQ ID NO: 1 and analogues thereof and a pharmaceutically acceptable carrier for use in treating **breast cancer or to reduce breast tumor size**, does not reasonably provide enablement for a composition comprising N-terminally truncated galectin-3 according to SEQ ID NO: 1 and analogues thereof and a pharmaceutically acceptable carrier for use in treating **rheumatoid arthritis, juvenile idiopathic arthritis, atherosclerotic cardiovascular disease and cancer or to reduce tumor size**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There

are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a composition comprising an effective amount of N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof and a pharmaceutically acceptable carrier for use in treating rheumatoid arthritis, juvenile idiopathic arthritis, atherosclerotic cardiovascular disease and cancer or to reduce tumor size.

This means that the claimed composition will be effective for treatment for all of these diverse diseases.

It is noted that the formulation of the composition for slow release reads on use as a pharmaceutical for treatment of disease.

The specification teaches that N-terminally truncated galectin-3/SEQ ID NO: 1 injected intramuscularly, twice daily reduced tumor volume and weight and tumor metastasis in mice injected subcutaneously with MDA-MB-435 human breast cancer cells that express galectin-3 (see Example 1, p. 48-56, and Figs. 6-9).

Additionally, the specification postulates that evidence suggests that in rheumatoid arthritis and juvenile idiopathic arthritis defective apoptosis of mononuclear phagocytic cells and activation of synovial fibroblasts is related to increased expression of galectin-3. The specification hypothesizes that a potential therapeutic agent for arthritis could be based on the inhibition of galectin-3. The specification hypothesizes that soluble recombinant N-terminally truncated galectin-3 competes with endogenous galectin-3 for carbohydrate binding sites in the extracellular matrix and cell-cell adhesions important in cellular invasion process and activation of immune cells through cross-linking carbohydrate expressing receptors on cell surfaces by multimerization mediated by the N-terminal domain. The specification hypothesizes that in arthritis N-terminally truncated galectin-3 is expected to be therapeutic by reducing the threshold for induction of apoptosis in some cells of the immune system that express and absorb galectin-3 from the extracellular milieu, and to reduce the activation of other cells such as neutrophils and synovial fibroblasts (see p. 75, lines 12-25).

Additionally, the specification teaches that organ biodistribution analyses showed that N-terminally truncated galectin-3 localized to the liver, kidney, and spleen but not to the heart or lungs (see p. 54, lines 13-16, and Figure 5).

The teachings of the specification cannot be extrapolated to the scope of the claims because no nexus has been established between the claimed composition and treating rheumatoid arthritis, juvenile idiopathic arthritis, atherosclerotic cardiovascular disease and cancers, other than breast cancer, and 1) the process of drug discovery is unpredictable and 2) cancers are heterogeneous in nature and 3) and the efficient targeting of diseased cells with the N-terminally truncated galectin-3C for treatment is unpredictable.

1) As drawn to the unpredictability of drug discovery it is well known that the art of that the development of new therapies is highly unpredictable. For example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients; see 3rd col., 2nd to last para. Furthermore, Feldmann and Steinman (Nature, 2005, 435:612-619) teach that in the pharmaceutical industry, drugs in only about 5% of the 'small molecule' drug projects end up as approved therapeutics (see p. 614, left col. 1st full para.). Furthermore, Feldmann and Steinmann teach that in selecting targets for treatment of autoimmune disease like rheumatoid arthritis, "A widespread misconception is that every step of the immune or proinflammatory process is a potential therapeutic target. Regrettably, this is not the case. Because most therapeutics only have a partial inhibitory effect, only those molecules that are in short supply (and thus rate-limiting) are likely to be useful targets (see p.612, right col.)." Additionally, Feldmann and Steinman teach that, " Although there is a lot of optimism . . . that many new safe therapies are just around the corner, this hope belies the fact that clinical successes, where the benefits outweigh the risks, are few and far between (see p. 617, right col.)."

Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the claimed composition would be

useful for treating rheumatoid arthritis, juvenile idiopathic arthritis, atherosclerotic cardiovascular disease and cancers, other than breast cancer, based on the specification as originally filed

2) As drawn to the heterogeneity of cancers, cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is expected and known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between N-terminally truncated galectin-3 and breast cancer cells, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No: 850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Furthermore Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols.

Given the above, it is clear that it is not possible to predictably extrapolate a correlation between N-terminally truncated galectin-3/SEQ ID NO: 1 therapy in any tumor type other than breast cancer, based on the information in the specification and known in the art without undue experimentation.

3) As drawn to targeting of diseased cells, the N-terminally truncated galectin-3/SEQ ID NO: 1 protein must accomplish several tasks to be effective for therapy. It must be delivered into the circulation that supplies the diseased tissue and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival and function despite action at the proper site for the N-terminally truncated galectin-3/SEQ ID NO: 1. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The N-terminally truncated galectin-3/SEQ ID NO: 1 may be inactivated *in vivo* before producing a sufficient effect or even binding to the target, for example, by degradation, immunological activation or due to an inherently short half-life of the protein. In addition, the protein may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the protein and a large enough local concentration may not be established. Although drawn to antibody immunotherapy, the teachings of White et al. (2001, Ann. Rev. Med., 2001, 52:125-145) are relevant to the use of the instant composition for treatment by its binding to target antigens. White et al. teach that for successful targeting and immunotherapy, besides specificity of the antibody for the antigen, other prosperities of the antigen should be

considered including the following: (1) the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating; and (2) whether antigens are shed, modulated, or internalized influences the effectiveness of the administered immunotherapy (i.e. the antibody) (p.125, 2nd para.).

Given what is know in the art and in the absence of additional guidance, for example *in vivo* data showing an effect of the claimed method using the N-terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof for treating rheumatoid arthritis, juvenile idiopathic arthritis, atherosclerotic cardiovascular disease and cancers, other than breast cancer, one could not predict that the claimed - terminally truncated galectin-3, which has a sequence according to SEQ ID NO: 1 and analogues thereof would be useful for treating said diseases.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of

guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

16. Claim 4 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of **atherosclerotic cardiovascular disease** has no clear support in the specification and the claims as originally filed. Examiner's review of the specification did not reveal support for the newly added limitation. Applicant is invited to submit evidence pointing to page and line number in the specification wherein support for the newly added limitation can be found. The subject matter claimed in claims 4 broadens the scope of the invention as originally disclosed in the specification.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Seetharaman et al. (Journal of Biological Chemistry, 1998 273: 13047-13052, as evidenced by SCORE search results 20070105_174341_us-10-726-198-1.50 aligns.rup and LEG3_HUMAN alignment below).

The claims are drawn to: 1) A composition comprising an effective amount of N-terminally truncated galectin-3 and a pharmaceutically acceptable carrier; 2) The composition according to claim 1, wherein said N-terminally truncated galectin-3 has a sequence according to SEQ ID NO: 1 and analogues thereof; 3) The composition according to claim 1, wherein said N-terminally truncated galectin-3 is present in an amount sufficient to reduce tumor size; 4) The composition according to claim 1 for use in for treating rheumatoid arthritis, juvenile idiopathic arthritis, atherosclerotic cardiovascular disease, and cancer; 7) The composition according to claim 1, wherein said composition is formulated for slow release.

It is noted that the recitation of the uses of the composition in claims 3, 4, and 7 are merely suggestive of intended uses and are not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredient *per se*, which is N-terminally truncated galectin-3 which has a sequence according to SEQ ID NO: 1 and analogues thereof.

It is noted that the specification teaches in the brief description of Figure 2 that N-terminally truncated galectin-3 is galectin-3C (see p. 14, lines 10-14).

Seetharaman et al. (J. Biol. Chem. 1998 273:13047-13052) teach galectin-3C which consists of residues 107-250 of human galectin-3 (see p. 13047, right col., *Protein Purification*

*and Crystallization*). One of skill in the art would immediately envision putting galectin-3C in a pharmaceutically acceptable carrier like phosphate buffered saline for the storage and use of the protein.

***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

18. Claims 1 and 2-4 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claim claims 1 and 2 of US Patent No.: 6,770,622. This is a double patenting rejection.

It is noted that claim 1 of US Patent NO: 6,770,622 is drawn to 'A composition comprising N-terminally truncated galectin-3 consisting of a sequence as set forth in SEQ ID No.:1 and a pharmaceutically acceptable carrier for treating cancer." and that claim 1 of the instant application is drawn to "A composition comprising an effective amount of A-terminally truncated galectin-3 and a pharmaceutically acceptable carrier." wherein the specification defines "an effective amount" for purposes herein is thus determined by such considerations as are known in the art of cancer treatment wherein it must be effective to provide measurable improvement in persons given the treatment, and, in a preferred embodiment, complete recovery of the patient without the presence of cancer cells (para 0112 of the published application), thus the scope of the two claims is identical.

Further, it is noted that the recitation of the uses of the composition in claims 3, 4, and in the instant application and claims 1 and 2 of US Patent No.: 6,770,622 are merely suggestive of intended uses and are not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredient *per se*, which is N-terminally truncated galectin-3 which has a sequence according to SEQ ID NO: 1.

19. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of 12/2/2003 for claim 4 for the instantly claimed application serial number 10/726,198, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access

to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR

SUSAN UNGAR, PH.D

```
LEG3_HUMAN
ID   LEG3_HUMAN     STANDARD;      PRT;   249 AA.
AC   P17931; Q16005; Q96J47;
DT   01-NOV-1990, integrated into UniProtKB/Swiss-Prot.
DT   01-NOV-1995, sequence version 3.
DT   07-MAR-2006, entry version 72.
DE   Galectin-3 (Galactose-specific lectin 3) (Mac-2 antigen) (IgE-binding
DE   protein) (35 kDa lectin) (Carbohydrate-binding protein 35) (CBP 35)
DE   (Laminin-binding protein) (Lectin L-29) (L-31) (Galactoside-binding
DE   protein) (GALBP).
GN   Name=LGALS3; Synonyms=MAC2;
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae;
OC   Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA].
RX   MEDLINE=91084480; PubMed=2261464;
RA   Robertson M.W., Albrandt K., Keller D., Liu F.-T.;
RT   "Human IgE-binding protein: a soluble lectin exhibiting a highly
RT   conserved interspecies sequence and differential recognition of IgE
RT   glycoforms.";
RL   Biochemistry 29:8093-8100(1990).
RN   [2]
RP   NUCLEOTIDE SEQUENCE [MRNA].
RC   TISSUE=Carcinoma;
RX   MEDLINE=90384999; PubMed=2402511;
RA   Cherayil B., Chaitovitz S., Wong C., Pillai S.;
RT   "Molecular cloning of a human macrophage lectin specific for
RT   galactose.";
RL   Proc. Natl. Acad. Sci. U.S.A. 87:7324-7328(1990).
RN   [3]
RP   NUCLEOTIDE SEQUENCE [MRNA].
RX   MEDLINE=91216471; PubMed=2022338; DOI=10.1016/0378-1119(91)90139-3;
RA   Oda Y., Leffler H., Sakakura Y., Kasai K., Barondes S.H.;
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RT "Human breast carcinoma cDNA encoding a galactoside-binding lectin
RT homologous to mouse Mac-2 antigen.";
RL Gene 99:279-283(1991).
RN [4]
RP NUCLEOTIDE SEQUENCE [MRNA].
RX MEDLINE=91183475; PubMed=2009535;
RA Raz A., Carmi P., Raz T., Hogan V., Mohamed A., Wolman S.R.;
RT "Molecular cloning and chromosomal mapping of a human galactoside-
RT binding protein.";
RL Cancer Res. 51:2173-2178(1991).
RN [5]
RP NUCLEOTIDE SEQUENCE [MRNA], AND SUBCELLULAR LOCATION.
RX MEDLINE=93234518; PubMed=7682704;
RA Lotz M.M., Andrews C.W. Jr., Korzelius C.A., Lee E.C.,
RA Steele G.D. Jr., Clarke A., Mercurio A.M.;
RT "Decreased expression of Mac-2 (carbohydrate binding protein 35) and
RT loss of its nuclear localization are associated with the neoplastic
RT progression of colon carcinoma.";
RL Proc. Natl. Acad. Sci. U.S.A. 90:3466-3470(1993).
RN [6]
RP NUCLEOTIDE SEQUENCE [GENOMIC DNA].
RX PubMed=9439577; DOI=10.1006/abbi.1997.0447;
RA Kadrofske M.M., Openo K.P., Wang J.L.;
RT "The human LGALS3 (galectin-3) gene: determination of the gene
RT structure and functional characterization of the promoter.";
RL Arch. Biochem. Biophys. 349:7-20(1998).
RN [7]
RP NUCLEOTIDE SEQUENCE [MRNA].
RC TISSUE=Gastric adenocarcinoma;
RA Kato S.;
RT "Human galectin-3 full-length cDNA.";
RL Submitted (AUG-1997) to the EMBL/GenBank/DDBJ databases.
RN [8]
RP NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA].
RC TISSUE=Skin;
RX MEDLINE=22388257; PubMed=12477932; DOI=10.1073/pnas.242603899;
RA Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G.,
RA Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D.,
RA Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K.,
RA Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,
RA Diatchenko L., Marusina K., Farmer A.A., Rubin G.M., Hong L.,
RA Stapleton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
RA Brownstein M.J., Usdin T.B., Toshiyuki S., Carninci P., Prange C.,
RA Raha S.S., Loquellano N.A., Peters G.J., Abramson R.D., Mullahy S.J.,
RA Bosak S.A., McEwan P.J., McKernan K.J., Malek J.A., Gunaratne P.H.,
RA Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.W.,
RA Villalon D.K., Muzny D.M., Sodergren E.J., Lu X., Gibbs R.A.,
RA Fahey J., Helton E., Ketteman M., Madan A., Rodrigues S., Sanchez A.,
RA Whiting M., Madan A., Young A.C., Shevchenko Y., Bouffard G.G.,
RA Blakesley R.W., Touchman J.W., Green E.D., Dickson M.C.,
RA Rodriguez A.C., Grimwood J., Schmutz J., Myers R.M.,
RA Butterfield Y.S.N., Krzywinski M.I., Skalska U., Smailus D.E.,
RA Schnerch A., Schein J.E., Jones S.J.M., Marra M.A.;
RT "Generation and initial analysis of more than 15,000 full-length human

RT and mouse cDNA sequences.";
RL Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).
RN [9]
RP PHOSPHORYLATION SITES SER-5 AND SER-11.
RX MEDLINE=94075369; PubMed=8253806;
RA Huflejt M.E., Turck C.W., Lindstedt R., Barondes S.H., Leffler H.;
RT "L-29, a soluble lactose-binding lectin, is phosphorylated on serine 6
RT and serine 12 in vivo and by casein kinase I.";
RL J. Biol. Chem. 268:26712-26718(1993).
RN [10]
RP INTERACTION WITH LGALS3BP.
RX MEDLINE=98169377; PubMed=9501082; DOI=10.1093/emboj/17.6.1606;
RA Sasaki T., Brakebusch C., Engel J., Timpl R.;
RT "Mac-2 binding protein is a cell-adhesive protein of the extracellular
RT matrix which self-assembles into ring-like structures and binds beta1
RT integrins, collagens and fibronectin.";
RL EMBO J. 17:1606-1613(1998).
RN [11]
RP INTERACTIONS WITH ITGB1; ITGA3 AND CSPG4, SUBCELLULAR LOCATION, AND
RP FUNCTION.
RX PubMed=15181153; DOI=10.1091/mbc.E04-03-0236;
RA Fukushi J., Makagiansar I.T., Stallcup W.B.;
RT "NG2 proteoglycan promotes endothelial cell motility and angiogenesis
RT via engagement of galectin-3 and alpha3beta1 integrin.";
RL Mol. Biol. Cell 15:3580-3590(2004).
RN [12]
RP X-RAY CRYSTALLOGRAPHY (2.1 ANGSTROMS) OF 113-249.
RX MEDLINE=98250755; PubMed=9582341; DOI=10.1074/jbc.273.21.13047;
**RA Seetharaman J., Kanigsberg A., Slaaby R., Leffler H., Barondes S.H.,**
**RA Rini J.M.;**
**RT "X-ray crystal structure of the human galectin-3 carbohydrate**
**RT recognition domain at 2.1-A resolution.";**
**RL J. Biol. Chem. 273:13047-13052(1998).**
CC **-!- FUNCTION: Galactose-specific lectin** which binds IgE. May mediate
CC with the alpha-3, beta-1 integrin the stimulation by CSPG4 of
CC endothelial cells migration.
CC -!- SUBUNIT: Probably forms homo- or heterodimers. Binds LGALS3BP.
CC Interacts with LYPD3 (By similarity). Forms a complex with ITGB1,
CC ITGA3 and CSPG4.
CC -!- SUBCELLULAR LOCATION: Nuclear. Cytoplasmic in adenomas and
CC carcinomas. May be secreted by a non-classical secretory pathway
CC and associate with the cell surface.
CC -!- TISSUE SPECIFICITY: A major expression is found in the colonic
CC epithelium. It is also abundant in the activated macrophages.
CC -!- SIMILARITY: Contains 1 galectin domain.
CC ----------

CC ----------
DR EMBL; M57710; AAA35607.1; -; mRNA.
DR EMBL; M35368; AAA88086.1; -; mRNA.
DR EMBL; M36682; AAA36163.1; -; mRNA.
DR EMBL; M64303; -; NOT_ANNOTATED_CDS; mRNA.
DR EMBL; S59012; AAB26229.1; -; mRNA.

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DR   EMBL; AF031425; AAB86584.1; -; Genomic_DNA.
DR   EMBL; AF031422; AAB86584.1; JOINED; Genomic_DNA.
DR   EMBL; AF031423; AAB86584.1; JOINED; Genomic_DNA.
DR   EMBL; AF031424; AAB86584.1; JOINED; Genomic_DNA.
DR   EMBL; AB006780; BAA22164.1; -; mRNA.
DR   EMBL; BC001120; AAH01120.1; -; mRNA.
DR   EMBL; BC053667; AAH53667.1; -; mRNA.
DR   PIR; A35820; A35820.
DR   PDB; 1A3K; X-ray; @=113-249.
DR   PDB; 1KJL; X-ray; A=104-249.
DR   PDB; 1KJR; X-ray; A=104-249.
DR   Ensembl; ENSG00000131981; Homo sapiens.
DR   H-InvDB; HIX0011683; -.
DR   HGNC; HGNC:6563; LGALS3.
DR   MIM; 153619; gene.
DR   LinkHub; P17931; -.
DR   GO; GO:0005886; C:plasma membrane; TAS.
DR   GO; GO:0005529; F:sugar binding; TAS.
DR   InterPro; IPR013320; ConA_like_subgrp.
DR   InterPro; IPR001079; Galectin_bd.
DR   Pfam; PF00337; Gal-bind_lectin; 1.
DR   SMART; SM00276; GLECT; 1.
DR   PROSITE; PS00309; GALAPTIN; 1.
KW   3D-structure; Acetylation; IgE-binding protein; Lectin;
KW   Nuclear protein; Phosphorylation; Polymorphism; Repeat.
FT   INIT_MET      0      0       By similarity.
FT   CHAIN         1    249       Galectin-3.
FT                                /FTId=PRO_0000076930.
FT   REPEAT       35     43       1.
FT   REPEAT       44     52       2.
FT   REPEAT       53     61       3.
FT   REPEAT       62     68       4 (approximate).
FT   REPEAT       69     77       5.
FT   REPEAT       78     87       6 (approximate).
FT   REPEAT       88     99       7 (approximate).
FT   REPEAT      100    108       8 (approximate).
FT   DOMAIN      117    249       Galectin.
FT   REGION       35    108       8 X 9 AA tandem repeats of Y-P-G-X(3)-P-
FT                                G-A.
FT   REGION      180    186       Beta-galactoside binding (By similarity).
FT   MOD_RES       1      1       N-acetylalanine (By similarity).
FT   MOD_RES       5      5       Phosphoserine (partial).
FT   MOD_RES      11     11       Phosphoserine (partial).
FT   DISULFID    172    172       Interchain (By similarity).
FT   VARIANT      63     63       H -> P (in dbSNP:4644).
FT                                /FTId=VAR_012988.
FT   VARIANT      97     97       P -> T (in dbSNP:1042188).
FT                                /FTId=VAR_012989.
FT   CONFLICT     32     51       AGGYPGASYPGAYPGQAPPG -> QGLPRGFLSWGLPRAGT
FT                                PR (in Ref. 2).
FT   CONFLICT     87     87       Missing (in Ref. 2).
FT   CONFLICT    231    231       S -> R (in Ref. 4).
FT   STRAND      113    113
FT   STRAND      115    120
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FT   TURN        122    123
FT   TURN        127    128
FT   STRAND      129    137

  Query Match             100.0%;  Score 754;  DB 1;  Length 249;
  Best Local Similarity   100.0%;  Pred. No. 9.5e-68;
  Matches  143;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 GAPAGPLIVPYNLPLPGGVVPRMLITILGTVKPNANRIALDFQRGNDVAFHFNPRFNENN 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        107 GAPAGPLIVPYNLPLPGGVVPRMLITILGTVKPNANRIALDFQRGNDVAFHFNPRFNENN 166

Qy         61 RRVIVCNTKLDNNWGREERQSVFPFESGKPFKIQVLVEPDHFKVAVNDAHLLQYNHRVKK 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        167 RRVIVCNTKLDNNWGREERQSVFPFESGKPFKIQVLVEPDHFKVAVNDAHLLQYNHRVKK 226

Qy        121 LNEISKLGISGDIDLTSASYTMI 143
              |||||||||||||||||||||||
Db        227 LNEISKLGISGDIDLTSASYTMI 249
```

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| APPLICATION NO. /CONTROL NO. | FILING DATE | FIRST NAMED INVENTOR / PATENT IN REEXAMINATION | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 10/726,198 | 12/02/2003 | Constance M. John | 3157.0001 |

| EXAMINER |
|---|
| Peter Reddig, Ph.D. |

| ART UNIT | PAPER |
|---|---|
| 1642 | |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant must provide the appropriate SEQ ID NO: for all sequences encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

If a complete reply has not been submitted by the time period set in the accompanying Office action has expired, this application will become abandoned under 37 CFR 1.821(g).

Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (http://ww.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual-ePAVE)

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Commissioner for Patents

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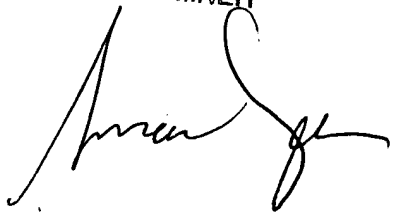
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foleycan be reached on 571-272-0890.

Peter Reddig, Ph.D.
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



| Notice to Comply | Application No. 10/726,198 | Applicant(s) John et al. | |
|---|---|---|---|
| | Examiner Peter J. Reddig | Art Unit 1642 | |

## NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The disclosure is lacking numerous sequence identifiers and sequence ID numbers, see the section titled "Sequence Listing" in the accompanying First Office Action on the Merits.

### Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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